Remarks in Support of Patentability

Rejection Under 35 USC 112

Claims 1-10 and 24-25 were rejected under 35 USC 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

Specifically, Claims 1, 24 and 25 were objected to due to the inclusion of the term "protected by" with reference to the binding moiety. These claims have been amended to specify that the chimeric protein-encoding portion of the recombinant polynucleotide is protected from degradation by a protein binding moiety that binds non-specifically to the polynucleotide irrespective of nucleotide sequence. With this amendment it is submitted that the Examiner's objection has been overcome, since the claim now clearly specifies that the protein binding moiety binds non-specifically to the polynucleotide in order to protect it from degradation. Basis for this amendment may be found on page 5, lines 19-22 and on page 18, lines 29-34 of the specification.

Claim 6 was objected to for being indefinite by reciting the term "can be". This claim has been amended to specify that the two or more nucleotide sequence motifs are each capable of being bound by the nucleotide binding portion of the chimeric protein.

Claim 24 has also been amended by deletion of the phrase "at least" with reference to the chimeric protein-coding portion, to clarify that the protein binding moiety binds to the polynucleotide to protect it from

degradation and to specify that at least one of the two nucleotide sequence motives present is bound by the nucleotide binding portion of the chimeric protein.

Rejections under 35 USC 102(b) and 35 USC 103(a)

The Examiner objected that Claims 1, 3-6, 8-10 and 25 were anticipated by US 5,498,530 (Schatz) or in an alternative were obvious over that document. The Examiner argues that Schatz teaches methods of generating a peptide library.

The claims in suit have been amended to specify that the construct is a peptide display carrier package and to specify that the target peptide is displayed on the exterior of the package. Claim 1 has also been amended to specify that the construct is produced by expression of the polynucleotide in a host cell and is expressed from the host cell without lysis thereof. None of these features are taught or suggested by Schatz. The present invention demonstrated the external display of functional peptides on the surface of a PDCP via a steroid receptor binding domain for the first time.

Claim 10 has been cancelled.

Basis to specify that the target peptide portion is displayed externally on the PDCP may be found in the specification at page 5, lines 17 to 22; page 6, lines 12 to 15; page 8, lines 2 to 5; and page 18, lines 20 to 25. Basis for the construct to be produced by a host cell by expression of the polynucleotide and extruded from the host cell without lysis thereof is found in claim 10, now

cancelled, and also at page 8, lines 5 to 12; page 14, lines 26 to 29; page 15, lines 29 to 34; and page 18, lines 29 to 34. No new matter has been added.

In the present invention, chimeric protein is incorporated into the peptide display carrier package and the entire vector is bound, and therefore protected from nucleotide degradation, by a binding moiety, namely a protein that binds to the polynucleotide in a non-sequence specific manner. Thus, that part of the vector not bound by the chimeric protein via its nucleotide binding portion is protected from degradation by the binding moiety, which is typically a viral coat protein such as a phage coat protein. The binding moiety can be encoded by a distinct and separate vector.

In the Schatz methodology a chimeric fusion protein is created that includes a DNA binding protein and a target peptide such that association between the recombinant DNA vector encoding the chimeric protein and the chimeric protein itself may occur in the cytoplasm of the host cell. Schatz fails to suggest that the DNA vector not bound by the chimeric protein should be protected from DNA degradation. In the screening method proposed by Schatz the host cell is lysed (see column 2, lines 53 to 56 of Schatz). During and prior to lysis of the host cell used by Schatz, the chimeric construct would inevitably mixed with nucleases and proteases in the host cell cytoplasm where the construct is assembled. Proteases and nucleases would also be released by lysis of the host cell. These nucleases would degrade the DNA vector and proteases would degrade the protein portion of the construct.

Thus, by contrast, Schatz uses the host cell to produce chimeric protein and DNA which must subsequently come into contact and bind in the cytoplasmic environment within the cell, but which would be degraded prior to and after cell lysis.

The methodology of Schatz is also limited to peptides that are functionally folded in the cytoplasm and this limitation would reduce the range of suitable peptides considerably. The methodology of Schatz inevitably results in a build up of potentially toxic proteins within the host cell.

Schatz et al recognize that the system described is further restricted in the screening/selection methods (panning), as this process has by necessity to be conducted under conditions that maintain the protein-DNA complex, and significant steps need to be taken to maintain the integrity of a sufficient proportion of these complexes (column 7, line 40 onwards). Schatz fails to take account of the inherent inefficiencies of the system described caused by the susceptibility of the polynucleotide to the action of nuclease/protease enzymes released from the host cell following lysis. Although steps can be taken to limit enzyme activity, these are never completely effective. The present invention in contrast provides for recombinant peptides stably displayed on the external surface of highly resilient bacteriophage, wherein the encoding polynucleotide is protected against nuclease degradation by viral coat proteins and the

polynucleotide-DNA binding domain interaction is effectively permanent. Furthermore the integrity of the host cells is maintained throughout.

The Examiner admits that Schatz does not teach that the chimeric protein encoding portion of the polynucleotide is protected by a protein, but alleges that use of bacteriophage as the vector would inevitably mean that the "chimeric protein encoding portion is considered as protected by coat protein". However, the methodology of Schatz described in the exemplification uses plasmid vector pMC5 and from Figure 2 clearly lacks a gene coding for functional viral coat protein as alleged by the Examiner. There is nothing within the teaching of Schatz which could indicate that viable coat protein was present at the time of production of the chimeric protein/DNA construct. One of ordinary skill in the art would be aware that a plasmid vector as used by Schatz cannot be packaged by a bacteriophage. Consequently the construct of Schatz could never be formed into a PDCP as required in current Claim 1 of the application.

Additionally, Schatz teaches that one of the steps required during library production, after initial purification using an antibody coated magnetic beads, is precipitation of the DNA using isopropanol (see column 26, lines 24-28). Isopropanol is a technique used in the art for precipitation of naked DNA. Thus, one of ordinary skill in the art would recognize that the construct of Schatz includes naked DNA, which can be so precipitated. Had the nucleotide construct of Schatz been formed into a PDCP, as is required in the current invention, such

precipitation would have involved the use of salt/polyethyleneglycol in place of isopropanol.

In conclusion, Schatz totally fails to teach formation of a PDCP nor that the target peptide may be expressed externally on such a PDCP. Additionally, as discussed above, the construct of Schatz is vulnerable to degradation both in the cell cytoplasm of the host cell and also after lysis. Host cell lysis is essential in the Schatz methodology for harvest of the construct. Both of these significant disadvantages are overcome using the construct as now claimed in the current application.

The Examiner also objected to Claims 1, 3-10 and 24-25 as obvious over a combination of Schatz and US 6,451,527 (Larocca). Larocca is cited for its reference to a steroid receptor as being able to bind certain DNA sequences. Specifically, Larocca teaches that to aid recovery of a phage genome, a DNA sequence able to bind to an appropriate protein (e.g. a steroid receptor) could be inserted into the phage genome. Consequently the genome, in the form of naked DNA, could be purified by exposure to a solid surface coated with that protein (see column 14, lines 12 to 18). Larocca teaches only that these DNA sequences can be inserted to assist purification of the naked DNA. Larocca never suggest that the gene encoding for the protein binding partner is inserted into the page genome, nor expressed therefrom. Thus neither Larocca nor Schatz teach the production of a PDCP, which is the subject of the application in suit.

Moreover, the methodology of Larocca involves the transfection of eukaryotic (mammalian) cells and is thus incompatible with production of a PDCP since phage cannot propagate in such cells. Larocca could not be combined with Schatz for this reason.

Even in combination, Schatz and Larocca do not suggest a PDCP as now claimed, nor do either of these documents suggest a PDCP in which the fusion protein is expressed on the surface and the nucleotide not bound by the chimeric protein is protected from degradation by a binding moiety.

Applicant believes that the application is now in condition for allowance and respectfully requests the issuance of a Notice of Allowance.

To the extent there is any fee required in connection with the receipt, acceptance and/or consideration of this paper and/or any accompanying papers submitted herewith, please charge all such fees to Deposit Account 50-1943.

Respectfully submitted,

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BY: Sherry Barag

DATE: September 9, 2005